# Primary chemo-radiotherapy for breast cancer patients who refused surgical treatment: a case series

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**Abstract:** Mastectomy or breast conserving surgery (BCS) followed by adjuvant radiotherapy (RT) and/ or chemotherapy plus hormone therapy is the current standard of care for breast cancer (BC). The disease usually progresses in patients who refuse any form of surgical intervention and notoriously impacts their life expectancy and quality. We collected 5 BC patients who refused any form of surgery and who received definitive RT or RT with chemotherapy (CCRT). The staging included early stage to locally advanced BCs according to criteria of the American Joint Committee on Cancer (AJCC) version 7. All patients achieved good local control. Only one had recurrence and was successfully salvaged by re-irradiation. The cosmetic effects were all satisfactory. Primary CCRT for BC patients who refuse surgery can be an effective alternative for achieving good survival and maintaining good quality of life.

Keywords: Breast cancer (BC); primary chemo-radiotherapy; radiotherapy (RT)

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## Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy in women worldwide. The epidemiology is similar in Taiwan, where the incidence is 1 in 120 women and is rising (1). Mastectomy or BCS follow by adjuvant radiotherapy (RT) and systemic chemotherapy is the mainstay of treatment for localized disease. Patients with locally advanced stage (stage III and up) usually receive neoadjuvant chemotherapy followed by surgery and adjuvant RT (2). A minority of patients, usually with medical comorbidity or by personal decision, refuse any form of surgical treatment, which substantially affects life expectancy. In the 1970s, this group of patients was treated with RT alone, with distant metastasis as the major cause of mortality (3).

With the advance in treatment strategies, cancer prognosis has improved dramatically in the past 20 years. Chemotherapy acts as a radiosensitizer to improve local control (LC) and survival over the use of RT alone. Primary concurrent chemoradiotherapy (CCRT) is the first choice in treating nasopharyngeal (4), locally advanced cervical (5) and anal cancers (6). However, CCRT is not the main "player" in the treatment for BC. Several phase III studies exploring the effect of CCRT in early BCs reported good LC but increased cardiac and pulmonary toxicities (7). In locally advanced BC, adjuvant CCRT resulted in a better locoregional recurrence free survival rate compared to sequential CCRT (8). A study from Japan also reported a pathologically complete response rate of 36% in 108 stage I to IIIA patients who received neoadjuvant CCRT (9).

The role of definitive CCRT has been reserved for patients who are older or cannot tolerate surgical treatment. Chargari *et al.* reported that a series of older early stage BC patients (>70 years, cT1-2N0) treated with RT alone achieved a promising 7-year LC rate of 95.8% (10). In the 1980s, De Lena *et al.* reported a similar treatment response in a randomized trial of chemotherapy followed by surgery

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or RT for locally advanced BC (11). The treatment response of definitive CCRT is acceptable; however, no randomized phase III trials have compared the effectiveness of primary CCRT to standard treatment.

Modern radiation techniques, which include stereotactic irradiation or intensity-modulated RT (IMRT), may deliver tumoricidal doses without severe complications. A 3-year overall survival (OS) rate of 93% and LC rate of 92% with favorable cosmetics outcome was achieved with definitive whole-breast irradiation followed by stereotactic body RT boost (12). In this case series, we report five cases of BC from our institution, who refused surgical treatment and achieved good LC with primary CCRT.

## **Case presentation**

From January 2010 to January 2014, five BC patients received definitive CCRT. All patients had the treatment strategy carefully explained to them, and provided their written informed consent to be included in this study. Clinical and image follow-up examinations were done regularly. This retrospective review was approved by our hospital Institutional Review Board, which found that it conformed to the provisions of the Declaration of Helsinki as revised in Edinburgh 2000. The stages presented were according to American Joint Committee on Cancer 7<sup>th</sup> edition (AJCC 7). The toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

Case 1 was a 56-year-old woman who presented with a growing, non-tender and fixed left inner upper quadrant breast mass of more than 6 months' duration in February 2013. Tumor biopsy reported invasive ductal carcinoma, cT2N1M0, AJCC 7 stage IIB with negative estrogen receptor (ER-), negative progesterone receptor (PR-), and positive human epidermal growth factor receptor 2 (HER2+). Positron emission tomography/computed tomography (PET/CT) scan showed an irregular left breast mass of 4.2 cm × 3.8 cm × 3 cm and involvement of the left axillary lymph node (Figure 1A). The clinical image staging was cT2N1M0, AJCC 7 stage IIB. The patient refused surgery and asked for nonsurgical treatment in our department. From May 2, 2013 to July 8, 2013, the patient received primary CCRT. Radiation consisted of 52.8 gray (Gy) in 24 fractions to the left breast and axilla lymph nodes with breast tumor bed boost to 76 Gy by tomotherapy and concurrent Tykerb (lapatinib). Adjuvant Herceptin (trastuzumab) and Xeloda (capecitabine) were

given for another 4 months. Only Grade 1 skin reaction was noted during the whole treatment course. The tumor was not seen on the images during follow-up scans at 4 months after treatment (*Figure 1B*). The representative radiation field is shown in *Figure 1C*. The patient remains free of disease.

Case 2 was a 63-year-old woman whose left BC was diagnosed in October 2011. The tumor was located at 3 o'clock and 4 cm from the left nipple (3/4 cm). Excisional biopsy reported invasive ductal carcinoma, ER+, PR- and HER2+. The patient discontinued conventional treatment for one year and returned in December 2012 with a protruded tumor mass and palpable lymph nodes. PET/CT scan showed a large left breast mass (5.3 cm) with central necrosis, skin invasion and involvement of multiple axillary lymph nodes, cT4dN3bM0, AJCC 7 stage IIIC (Figure 2A). The patient continued to insist on non-surgical treatment. From January 4, 2013 to April 19, 2013, the patient received definitive CCRT to the left breast and regional lymph nodes by tomotherapy with concurrent Herceptin (trastuzumab), Taxotere (docetaxel) and epirubicin. RT was withheld after 55 Gy over 22 fractions due to Grade 2 neutropenia and dermatitis. After the patient recovered, a second RT cycle of 12 Gy in 6 fractions was completed in April 2013. The total radiation dose to the breast tumor bed was 67 Gy in 31 fractions. The follow-up PET scan showed good treatment response (Figure 2B). The patient continued with Xeloda (capecitabine) and Navelbine (vinorelbine) for one more year. Until now, she remains disease free with good cosmetic outcomes.

Case 3 was a 46-year-old woman whose right BC was diagnosed in 2010. Biopsy reported invasive ductal carcinoma with ER+, PR+ and HER2-. Initially, the patient presented with skin involvement and multiple palpable axillary lymph nodes (cT4aN2a, AJCC 7 stage IIIB) (*Figure 3A*). The patient refused surgical treatment, and she received neoadjuvant chemotherapy with Taxol (paclitaxel) followed by definitive RT of 68 Gy over 36 fractions delivered by IMRT from July 2010 to October 2010. The patient remained disease free for 3 years. In April 2013, local recurrence was noted and was successfully salvaged by re-irradiation of the recurrent tumor bed of 62 Gy in 31 fractions in July 2013 (*Figure 3B*).

In 2014, the patient had a palpable left breast mass once again diagnosed with cancer. PET/CT scan showed a hypermetabolic left breast uptake of more than 5 cm (cT3N0M0, AJCC 7 stage IIB) (*Figure 3C*). From July 14, 2014 to October 13, 2014, the patient received a third RT



**Figure 1** Left breast cancer cT2N1M0 refused surgical treatment (A). She received definitive CCRT with complete remission of tumor (B). The representative radiation treatment field was shown in (C). CCRT, concurrent chemoradiotherapy.



**Figure 2** Left breast cancer who escaped treatment for one year with disease progression. Clinical staging was cT4dN3bM0 before treatment (A). Patient received primary CCRT with good local control for more than 5 years (B). CCRT, concurrent chemoradiotherapy.



Before treatment

After treatment

Figure 3 Right breast cancer, cT4aN2a before treatment (A), received primary CCRT 68 Gy with paclitaxel with disease recurrence 3 years later. Patient refused surgery and was re-irradiated. Tumor achieved complete remission until now (B). Patient was again diagnosed with left breast cancer in 2014 (C) and was successfully treated by definitive CCRT (D). CCRT, concurrent chemoradiotherapy.

course consisting of 64 Gy in 30 fractions by IMRT with concurrent biweekly cisplatin and maintenance Xeloda (capecitabine) for 1 more year after CCRT. The follow-up images showed no disease progression (*Figure 3D*).

Case 4 was a 39-year-old woman who presented with two palpable masses at 12/1 cm and 2/1 cm from the left nipple. A biopsy in December 2010 indicated invasive ductal carcinoma with ER+, PR+ and HER2-. PET/CT showed a 2.5 cm tumor with axillary lymph node metastases, cT2N1, AJCC 7 stage IIB (*Figure 4A*). The patient refused surgery and asked for organ preservation treatment. From March 14, 2011 to May 16, 2011, the patient completed definitive RT of 48 Gy in 24 fractions to the left breast with a boost up to 68 Gy to the tumor bed by tomotherapy. Chemotherapy consisted of triweekly Taxotere (docetaxel) (100 mg) and epirubicin (90 mg). The patient had complete remission of the tumor (*Figure 4B*). She continued on tamoxifen for another 5 years and remained in good clinical and cosmetic condition.

Case 5 was a 46-year-old woman with a palpable right breast mass noted in 2010. She did not receive any further examinations until the tumor size grew larger 2 years later.



Before treatment

After treatment

Figure 4 Left breast cancer, cT2N1 (A) who refused surgical treatment received primary CCRT with complete response (B). CCRT, concurrent chemoradiotherapy.



Before treatment

After treatment

Figure 5 Right breast cancer, cT3N0 (A) received primary CCRT with small residual nodule over her right breast (B). Patient eventually received mastectomy without apparent malignancies. CCRT, concurrent chemoradiotherapy.

Biopsy of the tumor reported invasive ductal carcinoma, ER+, PR+ and HER2-. The patient refused surgical treatment and sought organ preservation treatment. PET/ CT scan showed a 6 cm right breast tumor without lymph node involvement, cT3N0, AJCC 7 stage IIB (*Figure 5A*). The patient received definitive CCRT of 68 Gy in 36 fractions to the tumor bed by Tomotherapy concurrent with Taxotere (docetaxel) and epirubicin from May 15, 2012 to July 12, 2012. Treatment showed good therapeutic response (*Figure 5B*). Although the image examination was negative, the patient felt that a palpable nodule (less than 1 cm) persisted after irradiation. Eventually, a right mastectomy was performed in June 2013. Pathological studies showed no evident malignancies. The disease was well controlled and the patient remained in good health.

The characteristics of the five patients after CCRT are shown in *Table 1*. The five patients had an average age of 50 (range, 35–65) years. The BC stages were IIB to IIIC

		(AJCC 7) Stag	e Location (AJCC 7) Stag	tgnosis type Location (AJCC 7) Stag	e Diagnosis Histology Location INM type (AJCC 7) Stag
- ; - ; - ; - ; - ; - ;	E E	cT2N1M0 IIB EF	asive Left cT2N1M0 IIB EF ctal Hc cinoma	13/3 Invasive Left cT2N1M0 IIB EF ductal Hc carcinoma	2013/3 Invasive Left cT2N1M0 IIB EF ductal Hc carcinoma
В + ;- ег2 +	9 = EC	cT4dN3bM0 IIIC E	asive Left cT4dN3bM0 IIIC E ctal cinoma	11/10 Invasive Left cT4dN3bM0 IIIC E ductal carcinoma	2011/10 Invasive Left cT4dN3bM0 IIIC E ductal carcinoma
er2 -	Ш Щ	ti in 2010; cT4aN2a IIIB E n 2014 H	asive Right in 2010; cT4aN2a IIIB E ctal left in 2014 cinoma	10/5 Invasive Right in 2010; cT4aN2a IIIB E ductal left in 2014 carcinoma	2010/5 Invasive Right in 2010; cT4aN2a IIIB E ductal left in 2014 carcinoma
R +;- er2 +	Ш Н Ш	cT2N1M0 IIB E H	asive Left cT2N1M0 IIB E ctal cinoma	10/12 Invasive Left cT2N1M0 IIB E ductal carcinoma	2010/12 Invasive Left cT2N1M0 IIB E ductal carcinoma
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Table 1 Characteristics of 5 patients who received primary chemoradiotherapy

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according to AJCC 7. All patients refused to undergo any type of surgical treatment and all received RT over 60 Gy. One patient had Grade 2 skin reactions and neutropenia, which led to splitting the treatment courses. The concurrent chemotherapy regimens included different combinations of hormone antagonists and/or cytotoxic chemotherapeutics. Although one patient eventually underwent mastectomy, the specimen showed no evidence of residual tumor. The treatment toxicities were mainly dermatological. All patients had good cosmetic outcome and remained in good health.

### Discussion

In our case series, we showed that primary CCRT can achieve good disease control. Our report was limited by the small case number (5 patients in the 4-year period), but all had a good LC rate. The fast treatment responses correlated with good treatment response. In a similar study, in patients who achieved clinical complete response (cCR) by neoadjuvant chemotherapy, both surgery and RT yielded similar 5-year OS rates (74% by RT *vs.* 76% by surgery, P=0.9) (13).

CCRT is one of the most effective treatment options for locally advanced disease. BC, although sensitive to chemotherapy and RT, is not routinely treated with CCRT. Few studies have reported the results of primary CCRT to treat BC in either the early stage or locally advanced stages (*Table 2*). In unresectable locally advanced or inflammatory BC, primary CCRT can achieve a significant cCR rate. Patients who achieve complete or partial response can reserve salvage operation for residual disease or disease recurrence without compromising survival (14,15). Karasawa *et al.* reported a 2-year LC rate of 73.6% and 65.9% OS rate for unresectable BC patients treated with primary CCRT (16). The all five cases we reported achieved cCR after definitive CCRT.

In our case series, patients did not receive surgery rather they were nervous or delayed after the diagnosis of BC. In another study, more than 20% of locally advanced BC patients delayed seeking medical intervention for more than 4 weeks (17). In a series from Denmark, 157 patients with locally advanced BC who delayed treatment had a high correlation of severe medical or psychiatric co-morbidity. More than 20% ignored their obvious symptoms of BC (18). Data from the Taiwan Cancer Registry database indicated that, in 35,095 patients, the risk factors for delaying BC treatment were being older than 75 years, lower income and high comorbidity index (19). As presented, for patients who are reluctant to agree to surgery, RT or CCRT is a satisfactory alternative.

Approximately one-third of BC patients suffer from local relapse. Re-irradiation is a controversial treatment, because of the high cumulative doses to the chest wall. Unfortunately, the 5-year LC rate for re-excision was only 33% (20). Wahl et al. conducted a multi-institutional study of re-irradiation of an average 48 Gy. Of the 81 patients enrolled, the cCR rate was 60%. Only 3 had late Grade 3 and just 1 experienced Grade 4 skin toxicity (21). A German retrospective study of 42 BC patients reviewed the role of repeat surgery and adjuvant re-irradiation of 60 Gy after a previous dose of 54 Gy. The 5-year LC and OS rates were 62% and 60%, respectively. Eight patients suffered from Grade 3 skin toxicities without any Grade 4 events (22). Those studies point out that chest wall re-irradiation decreased the local failure rate with acceptable toxicities. Similarly, in case 3, the patient had excellent disease control with good cosmetic outcomes after re-irradiation of 62 Gy.

Radiation for BC may induce skeletal, pleural or pulmonary changes. It is not uncommon for small residual masses to persist for months or even years after RT. Palpable or visible small post-radiation nodules on the CT of patients with treated head and neck cancers is a common sequelae of endothelial proliferation and fibrotic changes (23). A Japanese study of 50 lung cancer patients with persistent nodules after stereotactic body RT showed a LC rate of 84% after a median follow up of 52 months. The persistence of the nodules did not always correlate with an increased risk of recurrence (24). Nonincreased PET uptake or stable sequential CT or magnetic resonance imaging findings are likely benign in patients whose clinical condition is stable. RT-induced thoracic changes are also seen physically or radiographically in skin, skeletal structures, the pleura (pleural thickening) and lungs (radiation pneumonitis and fibrosis) (25). In our case series, no patients had skin toxicities higher than Grade 2.

In conclusion, we have demonstrated that primary CCRT is an effective alternative treatment in patients who refuse surgery. In each case we reported, the disease was well-controlled with good quality of life and satisfactory cosmetic outcome. Until now, more than ten patients at our department had received this treatment strategy. All achieved good local control. We hope a randomized phase II or III trial to be launched to evaluate the real treatment efficacy.

Table 2 T	rials of primary C	CRT for breast c	ancers				
Studies	Study type	Patient number	Disease status	Treatment modality	RT dose	Chemotherapy/hormone therapy	Response rate
Mukai <i>et al.</i> (9)	Single arm phase II	108	Stage I–IIIA	Neoadjuvant CCRT follow by surgery 12–16 weeks later	45 Gy in 25 fractions (fx) with 10 Gy boost in 5 fx	Doxorubicin 60 mg/m <sup>2</sup> + cyclophosphamide 600 mg/m <sup>2</sup> (AC) x4 follow by weekly paclitaxel 80 mg/m <sup>2</sup> x12	pCR rate is 36%. pCR rate in HR-/Her-2 +: 57%. pCR rate in triple-: 52%
Chargari <i>et al.</i> (10)	Retrospective	396 (>70 years old)	T1-2	Definitive hypo- fractionated radiotherapy	32.5 Gy/5 fx/5 weeks follow by 13 Gy/2 fx boost	Hormone therapy for positive	Cause-specific survival: 96.4%; metastasis-free survival: 92.4%; loco-regional control: 95.8%
De Lena <i>et al.</i> (11)	Randomized	132	Locally advanced disease	Chemotherapy + RT vs. chemotherapy + mastectomy	1	Adriamycin plus vincristine (AV) for 10 cycles	Local control 75% in both groups
Shibamot <i>et al.</i> (12)	o Retrospective	8	Operable IA to IIIC patients	Whole breast RT follow by Stereotactic body radiotherapy boost	<ul> <li>50 Gy in 25 fractions</li> <li>follow by boost with</li> <li>18 to 25.5 Gy in 3 fx</li> <li>and 20 Gy in 8 fx</li> </ul>	Hormone given o 9 patients. Chemotherapy given to 4 patients	3-year overall survival: 93%; 3-year progression-free survival: 85%; 3-year local control: and 92%
Ring <i>et al.</i> (13)	Retrospective	136	Operable breast carcinoma	Neoadjuvant chemotherapy follow by surgery or radiotherapy	46 to 50 Gy follow by 11.1 to 17.5 Gy boost	Anthracycline-based regimens	Similar response between surgery and RT. 10-year disease free survival and overall survival: 60% vs. 70%
Bates et al. (14)	Retrospective	123	(l) Non-metastatic locally advanced; (ll) inflammatory BC (>3 cm); (ll) T4 disease	Primary chemotherapy followed by radiotherapy and surgery for residual disease	40 Gy in 15 fx with 10 Gy boost	AC x6 or 5 FU 600 mg/m², Epirubicin 75 mg/m² & cyclophosphamide 600 mg/m² every 3 weeks x6	Complete clinical response in 65%. Local recurrence: 13.5% vs. 17% (RT alone). 5-year overall survival: 54%. 5-year disease free survival: 43%
Kao <i>et al.</i> (15)	Phase //II trial	33	(l) Unresectable locally advanced or inflammatory breast cancers (T4N0-3M0-1); (ll) locally recurrent	CCRT follow by mastectomy if operable	60-70 Gy in a week-on/week-off schedule	Concurrent paclitaxel +/- vinorelbine	47% had pCR. 4-year locoregional control: 83%. 4-year disease-free survival: 33%. 4-year overall survival: 56%
Karasawa et al. (16)	Retrospective	39	Unresectable T4 BC	CCRT	RT dose of 59–66 Gy	All received chemotherapy and/or endocrine therapy following CCRT	2-year overall local control rate: 73.6%. 2-year survival rate: 65.9%
CCRT, co	ncurrent chemora	adiotherapy; BC,	, breast cancer; RT,	, radiotherapy.			

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# Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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